Studies toward the Pharmacophore of Salvinorin A, a Potent κ Opioid Receptor Agonist

Thomas A. Munro, Mark A. Rizzacasa, Bryan L. Roth, Beth A. Toth, and Feng Yan

Supporting Information

Table of Contents

Experimental Section.

Optical rotations: JASCO DIP-1000 digital polarimeter. IR spectra: Bio-Rad FTS 165 FT-IR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz): Varian Inova 400 and Unity Plus 400. HRESIMS: Bruker 4.7T BiOAPEX FTMS. TLC: Merck silica gel 60 F_{254} plates, visualized with phosphomolybdic acid in EtOH unless otherwise indicated ($hR_f = R_f \times 100$). HPLC: Spherex 5 μm silica column (250 × 10 mm), flow rate 2 mL min^{-1}. Flash column chromatography (FCC): 6 mL of Scharlau silica gel 60 (particle size 0.04 – 0.06 mm). Commercial ethanethiol and DMPU (Aldrich, 98%) were stored over 4Å sieves. 'Petrol' refers to the fraction boiling at 40-60 °C. 'Standard drying' refers to drying over $MgSO_4$, filtration and evaporation under reduced pressure.

Radioligand Binding Assays. Performed as previously detailed[1-3] using cloned receptors stably expressed in HEK 293 cells. **κ**: rat KORs with [^{3}H]diprenorphine (50 Ci/mmol, PerkinElmer Inc) or [^{3}H]U69,593 (41.4 Ci/mmol, PerkinElmer Inc) as radioligand. **δ**: human DORs with [^{3}H]DADLE {Enkephalin (2-D-Alanine-5-D-Leucine), [Tyrosyl-3,5-^{3}H(N)]-} (51.5 Ci/mmol, PerkinElmer Inc) as radioligand. **μ**: human MORs with [^{3}H]diprenorphine as radioligand. K_i values were calculated using Prism 4.01 (GraphPad Software, Inc) as the mean ±SEM of quadruplicate ($n \geq 4$) determinations. Nonspecific binding was defined using 10 μM naloxone.

Calcium Flux Functional Assay. Performed as previously detailed[4,5] using cloned rat KORs stably expressed in HEK 293 cells, cotransfected with the universal G protein $G\alpha_{16}$. Ca^{2+} mobilization was quantified using a 96-well FlexStationII with the calcium flux assay kit (Molecular Devices Corp, Sunnyvale, CA). EC_{50} and E_{max} values were calculated using Prism 4.01 (GraphPad Software, Inc), as the mean ±SEM of quadruplicate ($n \geq 4$) determinations.

Salvinorin A (1). ^{1}H NMR ($CDCl_3$): δ 7.40 (1H, br s, H-16), 7.38 (1H, t, *J* = 1.8 Hz, H-15), 6.37 (1H, dd, *J* = 1.8, 0.8 Hz, H-14), 5.51 (1H, dd, *J* = 11.7, 5.3 Hz, H-12), 5.13 (1H, m, H-2), 3.72 (3H, s, CO_2CH_3), 2.75 (1H, m, H-4), 2.49 (1H, dd, *J* = 13.5, 5.3 Hz, H-11a), 2.29 (2H, m, H-3), 2.17 (1H, br s, H-10), 2.16 (3H, s, $OCOCH_3$), 2.15 (1H, m, H-7a), 2.07 (1H, dd, *J* = 11.6, 3.1 Hz, H-8), 1.78 (1H, m, H-6a), 1.63 (1H, m, H-7b), 1.57 (1H, m, H-6b), 1.57 (1H, ddd, *J* = 13.5, 11.7, 0.8 Hz, H-11b), 1.44 (3H, s, H-20), 1.10 (3H, s, H-19).

8-*epi*-Salvinorin A (8-*epi*-**1).** Distilled DMPU (60 °C / 0.1 mmHg) was added to **1** (21.4 mg, 49.5 μmol) and $NaHCO_3$ (30.1 mg, 358 μmol), and stirred at 150 °C for 2 h. The resultant amber solution was cooled to rt, diluted in EtOAc, neutralized dropwise with 10% HCl, and washed (10% HCl × 4, then brine). Standard drying followed by FCC (30% - 50% EtOAc/petrol gradient) monitored by TLC (hR_f = 40 (**1**), 50 (8-*epi*-**1**) in Et_2O) gave 8-*epi*-**1** as a clear resin (10.8 mg, 51% (81% borsm)); $[\alpha]^{13}_{D}$ -53° (*c* 0.6, $CHCl_3$); **FTIR (film):** 2951, 1732, 1238, 1202, 1161, 876 cm^{-1}; **^{1}H NMR ($CDCl_3$):** δ 7.43 (1H, br s, H-16), 7.38 (1H, t, *J* = 1.7 Hz, H-15), 6.37 (1H, d, *J* = 1.7 Hz, H-14), 5.25 (1H, dd, *J* = 12.0, 2.2 Hz, H-12), 5.09 (1H, m, H-2), 3.69 (3H, s, CO_2CH_3), 2.75 (1H, m, H-4), 2.45 (1H, dd, *J* = 5.0, 2.2 Hz, H-8), 2.36 (1H, dd, *J* = 15.0, 2.2 Hz, H-11a), 2.26 (2H, m, H-3), 2.24 (1H, br s, H-10), 2.17 (1H, m, H-7a), 2.15 (3H, s, $OCOCH_3$), 2.00 (1H, td, *J* = 13.7, 3.9 Hz, H-6a), 1.83 (1H, tdd, *J* = 14.2, 5.0, 3.9 Hz, H-7b), 1.62 (3H, s, H-20), 1.54 (1H, dt, *J* = 13.7, 3.4 Hz, H-6b), 1.50 (1H, dd, *J* = 15.0, 12.0 Hz, H-11b), 1.07 (3H, s, H-19);

^{13}C NMR ($CDCl_3$): δ 202.3 (C, C-1), 173.4 (C, C-17), 171.8 (C, C-18), 169.8 (C, O*C*OCH$_3$), 143.6 (CH, C-15), 139.7 (CH, C-16), 123.3 (C, C-13), 108.5 (CH, C-14), 75.2 (CH, C-2), 70.1 (CH, C-12), 64.1 (CH, C-10), 52.9 (CH, C-4), 51.8 (CH$_3$, CO$_2$*C*H$_3$), 48.0 (CH$_2$, C-11), 45.2 (CH, C-8), 42.2 (C, C-5), 34.7 (C, C-9), 33.9 (CH$_2$, C-6), 30.6 (CH$_2$, C-3), 24.6 (CH$_3$, C-20), 20.5 (CH$_3$, OCO*C*H$_3$), 17.6 (CH$_2$, C-7), 15.2 (CH$_3$, C-19); **HRESIMS** [M + Na$^+$] *m/z* 455.1683 (calcd for $C_{23}H_{28}O_8Na^+$, 455.1676).

Salvinorin B formate (**3**). A mixture of Ac_2O (0.25 mL) and HCO_2H (0.7 mL) was stirred at 45 °C for 40 minutes. Pyridine (1 mL) was added to **2** (18.0 mg, 46.1 μmol), warmed to 45 °C until fully dissolved, then cooled to 0 °C. The cooled anhydride mixture was added dropwise by pipette, causing violent bubbling. The solution was warmed to room temperature and stirred for 30 minutes, when TLC indicated completion (hR_f = 85 (**3**), 65 (**2**) in 20% acetone/CH_2Cl_2, visualized in $KMnO_4$). The reaction mixture was cooled to 0 °C, diluted dropwise with water, and extracted into EtOAc. The organic layer was washed (1% HCl, water, 5% $NaHCO_3$ and brine). Standard drying and FCC (2-4% MeOH/CH_2Cl_2 gradient) gave **3** as a clear resin (13.8 mg, 72%); $[\alpha]^{26}_D$ -54° (*c* 0.6, CH_2Cl_2); **FTIR (film):** 2952, 1726, 1278, 1163, 875 cm^{-1}; **^{1}H NMR ($CDCl_3$):** δ 8.14 (1H, s, C*H*O), 7.41 (1H, br s, H-16), 7.40 (1H, t, *J* = 1.8 Hz, H-15), 6.38 (1H, dd, *J* = 1.8, 0.9 Hz, H-14), 5.54 (1H, dd, *J* = 11.7, 5.2 Hz, H-12), 5.26 (1H, m, H-2), 3.73 (3H, s, CO$_2$C*H*$_3$), 2.76 (1H, m, H-4), 2.51 (1H, dd, *J* = 13.5, 5.2 Hz, H-11a), 2.35 (2H, m, H-3), 2.18 (1H, d, *J* = 0.8 Hz, H-10), 2.17 (1H, m, H-7a), 2.08 (1H, dd, *J* = 11.5, 3.0 Hz, H-8), 1.80 (1H, m, H-6a), 1.67 (1H, m, H-7b), 1.58 (1H, ddd, *J* = 13.5, 11.7, 0.8 Hz, H-11b), 1.58 (1H, m, H-6b), 1.46 (3H, s, H-20), 1.13 (3H, s, H-19); **^{13}C NMR ($CDCl_3$):** δ 200.8 (C, C-1), 171.4 (C, C-18), 171.0 (C, C-17), 159.4 (CH, *C*HO), 143.7 (CH, C-15), 139.4 (CH, C-16), 125.1 (C, C-13), 108.3 (CH, C-14), 74.5 (CH, C-2), 72.0 (CH, C-12), 64.1 (CH, C-10), 53.5 (CH, C-4), 52.0 (CH$_3$, CO$_2$*C*H$_3$), 51.3 (CH, C-8), 43.4 (CH$_2$, C-11), 42.1 (C, C-5), 38.1 (CH$_2$, C-6), 35.5 (C, C-9), 30.6 (CH$_2$, C-3), 18.1 (CH$_2$, C-7), 16.4 (CH$_3$, C-19), 15.2 (CH$_3$, C-20); **HRESIMS** [M + Na$^+$] *m/z* 441.1525 (calcd for $C_{22}H_{26}O_8Na^+$, 441.1520).

13,14,15,16-Tetrahydrosalvinorin A (10). To a solution of **1** (20.3 mg, 46.9 μmol) in 50% CH_2Cl_2/MeOH (6 mL) was added 5% Rh/C (25.3 mg), and the suspension agitated under H_2 (4 atm) at room temperature for 90 minutes, when TLC indicated completion (*hRf* = 46 (**10**), 74 (**1**) in 20% acetone/CH_2Cl_2). The solution was filtered through diatomite filter aid and evaporated in vacuo. FCC (10% acetone/$CHCl_3$) gave **10** (13-epimers, 1:1) as a clear resin (12 mg, 59%). For characterisation, the less polar epimer was separated by HPLC in EtOAc; $[\alpha]^{19}_D$ -39° (*c* 0.4, $CHCl_3$); **FTIR (film):** 2953, 1730, 1235, 1165 cm^{-1}; **^{1}H NMR ($CDCl_3$):** δ 5.14 (1H, dd, *J* = 11.4, 8.6 Hz, H-2), 4.44 (1H, ddd, *J* = 11.7, 6.9, 5.0 Hz, H-12), 3.85 (1H, td, *J* = 8.5, 5.0 Hz, H-15a), 3.78 (1H, dd, *J* = 9.0, 7.6 Hz, H-16a), 3.74 (1H, dt, *J* = 8.5, 7.4 Hz, H-15b), 3.72 (3H, s, CO$_2$C*H*$_3$), 3.54 (1H, dd, *J* = 9.0, 6.7 Hz, H-16b), 2.73 (1H, m, H-4), 2.43 (1H, m, H-13), 2.30 (2H, m, H-3), 2.19 (1H, dd, *J* = 13.3, 5.0 Hz, H-11a), 2.17 (3H, s, OCOC*H*$_3$), 2.15 (1H, m, H-7a), 2.12 (1H, br s, H-10), 2.08 (1H, dddd, *J* = 12.6, 8.7, 7.4, 5.0 Hz, H-14a), 1.95 (1H, dd, *J* = 11.5, 3.1 Hz, H-8), 1.81 (1H, ddt, *J* = 12.6, 8.3, 7.4 Hz, H-14b), 1.76 (1H, m, H-6a), 1.60 (1H, m, H-7b), 1.54 (1H, m, H-6b), 1.35 (3H, s, H-20), 1.26 (1H, ddd, *J* = 13.3, 11.7, 0.8 Hz, H-11b), 1.09 (3H, s, H-19); **^{13}C NMR ($CDCl_3$):** δ 202.0 (C, C-1), 171.5 (C, C-18), 171.3 (C, C-17), 169.9 (C, O*C*OCH$_3$), 78.2 (CH, C-12), 75.0 (CH, C-2), 68.8 (CH$_2$, C-16), 68.0 (CH$_2$, C-15), 64.0 (CH, C-10), 53.5 (CH, C-4), 52.0 (CH$_3$,

CO_2CH_3), 51.4 (CH, C-8), 45.1 (CH, C-13), 42.0 (C, C-5), 41.2 (CH_2, C-11), 38.1 (CH_2, C-6), 35.1 (C, C-9), 30.8 (CH_2, C-3), 28.2 (CH_2, C-14), 20.6 (CH_3, $OCOCH_3$), 18.1 (CH_2, C-7), 16.3 (CH_3, C-19), 15.1 (CH_3, C-20); **HRESIMS** [M + Na^+] *m/z* 459.1984 (calcd for $C_{23}H_{32}O_8Na^+$, 459.1989).

Salvinorin A lactol (11). A solution of **1** (15.8 mg, 36.5 μmol) in dry THF (1 mL) was warmed until fully dissolved, then cooled to -78 °C. DIBALH (1M in THF, 0.5 mL, 500 μmol) was added dropwise. The solution was stirred for 25 minutes, then quenched (sat. aq. NH_4Cl dropwise), evaporated in vacuo until thick, diluted in water and extracted into Et_2O (× 3). Washing (sat. aq. NaCl), standard drying and FCC (6-10% acetone/CH_2Cl_2 gradient) monitored by TLC (*hRf* = 28 (**11**), 64 (**1**) in 10% acetone/CH_2Cl_2) gave **11** as a clear resin (10.4 mg, 65% (81% borsm)); **FTIR (film):** 3446, 2953, 1730, 1237, 1161, 875 cm^{-1}; **^{1}H NMR, major (17β) anomer ($CDCl_3$):** δ 7.36 (1H, br s, H-16), 7.34 (1H, t, *J* = 1.8 Hz, H-15), 6.38 (1H, dd, *J* = 1.8, 0.9 Hz, H-14), 5.12 (1H, m, H-2), 4.87 (1H, dd, *J* = 11.6, 2.4 Hz, H-12), 4.80 (1H, d, *J* = 8.7 Hz, H-17), 3.70 (3H, s, CO_2CH_3), 2.74 (1H, m, H-4), 2.25 (2H, m, H-3), 2.14 (3H, s, $OCOCH_3$), 2.11 (1H, dd, *J* = 13.2, 2.4 Hz, H-11a), 2.07 (1H, d, *J* = 0.9 Hz, H-10), 1.80 (1H, ddd, *J* = 13.8, 6.9, 3.2 Hz, H-7a), 1.70 (1H, dt, *J* = 13.5, 3.2 Hz, H-6a), 1.58 (1H, m, H-6b), 1.38 (3H, s, H-20), 1.37 (1H, m, H-7b), 1.21 (1H, ddd, *J* = 13.2, 11.6, 0.9 Hz, H-11b), 1.12 (1H, m, H-8), 1.08 (3H, s, H-19); **^{13}C NMR, major (17β) anomer ($CDCl_3$):** δ 202.5 (C, C-1), 171.9 (C, C-18), 169.9 (C, $OCOCH_3$), 143.0 (CH, C-15), 139.1 (CH, C-16), 126.2 (C, C-13), 108.8 (CH, C-14), 94.2 (CH, C-17), 75.0 (CH, C-2), 66.2 (CH, C-12), 65.4 (CH, C-10), 53.6 (CH, C-4), 52.1 (CH, C-8), 51.8 (CH_3, CO_2CH_3), 44.7 (CH_2, C-11), 42.4 (C, C-5), 38.8 (CH_2, C-6), 35.6 (C, C-9), 30.8 (CH_2, C-3), 20.6 (CH_3, $OCOCH_3$), 17.6 (CH_2, C-7), 16.7 (CH_3, C-19), 15.0 (CH_3, C-20).

17-Deoxysalvinorin A (12). To a stirred solution of lactol **11** (18.3 mg, 42.1 μmol), in dry CH_2Cl_2 (1 mL) under Ar, was added Et_3SiH (20 μL, 125 μmol). The solution was cooled to 0 °C, and BF_3•Et_2O (10 μL, 79 μmol) was added. The light brown solution was stirred at 0 °C for 2 h, when TLC indicated completion (*hRf* = 72 (**12**/**13**), 38 (**11**) in 10% acetone/CH_2Cl_2; 24 (**12**), 42 (**13**) in 2% acetone/CH_2Cl_2). The reaction was quenched (0.5 mL sat. $NaHCO_3$), and partitioned between Et_2O and brine. Standard drying and FCC (0-4% acetone/CH_2Cl_2 gradient) gave enol ether **13** (4.1 mg, 23%) along with **12** as a clear resin (8.4 mg, 48%); $[\alpha]^{20}_D$ -81° (*c* 0.4, CH_2Cl_2); **FTIR (film):** 2950, 1730, 1236, 1201, 1161, 875 cm^{-1}; **^{1}H NMR ($CDCl_3$):** δ 7.33 (2H, m, H-15 & 16), 6.34 (1H, t, *J* = 1.4 Hz, H-14), 5.14 (1H, dd, *J* = 10.7, 9.4 Hz, H-2), 4.70 (1H, dd, *J* = 11.6, 2.5 Hz, H-12), 3.70 (3H, s, CO_2CH_3), 3.58 (2H, d, *J* = 7.6 Hz, H-17), 2.77 (1H, m, H-4), 2.26 (2H, m, H-3), 2.15 (3H, s, $OCOCH_3$), 2.12 (1H, dd, *J* = 13.1, 2.6 Hz, H-11a), 2.09 (1H, d, *J* = 1.0 Hz, H-10), 1.66 (2H, m, H-6), 1.48 (1H, m, H-8), 1.38 (3H, s, H-20), 1.30 (2H, m, H-7), 1.19 (1H, ddd, *J* = 13.1, 11.6, 1.0 Hz, H-11b), 1.08 (3H, s, H-19); **^{13}C NMR ($CDCl_3$):** δ 202.5 (C, C-1), 171.9 (C, C-18), 169.9 (C, $OCOCH_3$), 142.9 (CH, C-15), 138.9 (CH, C-16), 127.0 (C, C-13), 108.7 (CH, C-14), 75.0 (CH, C-2), 67.5 (CH, C-12), 67.1 (CH_2, C-17), 65.6 (CH, C-10), 53.8 (CH, C-4), 51.8 (CH_3, CO_2CH_3), 46.4 (CH, C-8), 45.4 (CH_2, C-11), 42.7 (C, C-5), 39.0 (CH_2, C-6), 34.6 (C, C-9), 30.8 (CH_2, C-3), 20.6 (CH_3, $OCOCH_3$), 19.6 (CH_2, C-7), 16.8 (CH_3, C-19), 13.7 (CH_3, C-20); **HRESIMS** [M + Na^+] *m/z* 441.1881 (calcd for $C_{23}H_{30}O_7Na^+$, 441.1884).

8,17-Didehydro-17-deoxysalvinorin A (13). To a solution of lactol **11** (15.1 mg, 34.7 μmol) in

CH_2Cl_2 were added Et_3SiH (25 μL, 156 μmol) and Amberlyst 15 resin (22 mg). The sealed flask was stirred at rt for 24 h. Filtration, evaporation and FCC (1% acetone/CH_2Cl_2) gave **13** as a clear resin (11.0 mg, 76%); $[\alpha]^{23}_D$ -60° (*c* 0.5, CH_2Cl_2); **FTIR (film):** 2927, 1731, 1237, 1203, 1164, 875 cm^{-1}; **^{1}H NMR ($CDCl_3$):** δ 7.38 (1H, br s, H-16), 7.36 (1H, t, *J* = 1.9 Hz, H-15), 6.36 (1H, dd, *J* = 1.9, 0.8 Hz, H-14), 6.26 (1H, d, *J* = 1.8 Hz, H-17), 5.12 (1H, dd, *J* = 11.0, 9.0 Hz, H-2), 4.78 (1H, dd, *J* = 11.7, 2.1 Hz, H-12), 3.70 (3H, s, CO_2CH_3), 2.72 (1H, m, H-4), 2.33 (1H, dd, *J* = 13.6, 2.1 Hz, H-11a), 2.28 (2H, m, H-3), 2.27 (1H, m, H-7a), 2.16 (3H, s, $OCOCH_3$), 2.12 (1H, d, *J* = 0.8 Hz, H-10), 1.94 (1H, ddd, *J* = 14.6, 4.6, 2.6 Hz, H-7b), 1.69 (1H, ddd, *J* = 13.2, 4.4, 2.6 Hz, H-6a), 1.52 (3H, s, H-20), 1.50 (1H, td, *J* = 13.2, 4.6 Hz, H-6b), 1.40 (1H, ddd, *J* = 13.6, 11.6, 0.8 Hz, H-11b), 1.15 (3H, s, H-19); **^{13}C NMR ($CDCl_3$):** δ 202.9 (C, C-1), 172.0 (C, C-18), 169.9 (C, $OCOCH_3$), 143.2 (CH, C-15), 139.3 (CH, C-16), 137.1 (CH, C-17), 125.8 (C, C-13), 117.0 (C, C-8), 108.7 (CH, C-14), 75.2 (CH, C-2), 66.6 (CH, C-12), 65.5 (CH, C-10), 53.5 (CH, C-4), 51.7 (CH_3, CO_2CH_3), 44.4 (CH_2, C-11), 42.8 (C, C-5), 40.1 (CH_2, C-6), 34.1 (C, C-9), 30.6 (CH_2, C-3), 22.8 (CH_3, C-20), 22.6 (CH_2, C-7), 20.6 (CH_3, $OCOCH_3$), 15.4 (CH_3, C-19); **HRESIMS** [M + Na^+] *m/z* 439.1728 (calcd for $C_{23}H_{28}O_7Na^+$, 439.1727).

***O*-Demethyl-18-deoxysalvinorin A (15).** To dry EtSH (1.5 mL, 20.2 mmol) at 0 °C, stirred rapidly under a stream of Ar, was added n-BuLi in hexanes (2.1M, 8 mL, 16.9 mmol). Immediate, violent gas evolution was accompanied by the sudden formation of white solid. The flask was swirled, mixing the precipitate into a slurry, and rapid stirring continued while the remaining n-BuLi was added. After warming to room temperature, the solution was evaporated under reduced pressure, and finally dried under high vacuum at 50 °C for 30 min, giving LiSEt as a white powder.

1 (42.2 mg, 97.6 μmol) and LiSEt (13.7 mg, 201 μmol) under Ar were dissolved in DMPU (1 mL). The yellow solution was stirred at 55 °C for 23 h, when TLC indicated consumption of **1** and intermediate **2** (*hRf* = 0 smearing to 20 (**14**), 63 (**2**), 71 (**1**) in 1% H_2SO_4/10% MeOH/CH_2Cl_2). The cooled solution was diluted in EtOAc and washed (10% HCl × 3, then water), then extracted into 1% $NaHCO_3$ (× 3). The pooled aqueous fractions were acidified at 0 °C with 10% HCl, then extracted into CH_2Cl_2 (× 3). Standard drying gave an amber resin, which was treated with Ac_2O (0.4 mL) in pyridine (1 mL) and catalytic DMAP at room temperature for 17 h. After cooling to 0 °C and quenching (water), the solution was diluted in EtOAc and washed (10% HCl and sat. NH_4Cl). Standard drying gave acids **14** (H-8α:β, ~1.4:1) as an amber resin (29.7 mg, 73% over two steps). The mixed acids (35.2 mg, 84.0 μmol) were stirred in dry THF (1 mL) under Ar in a flask fitted with a reflux condenser. BH_3•THF (1.0 M, 110 μL, 110 μmol) was added dropwise; the solution was heated to 55 °C and stirred at this temperature for 90 minutes, when TLC indicated completion (*hRf* = 0 smearing to 30 (**14**), 56 (**15,** 8-*epi*-**15**) in 1% NEt_3/EtOAc). The solution was cooled to room temperature, quenched with water (dropwise), and evaporated in vacuo to give a cloudy paste. This was diluted in sat. $NaHCO_3$ and extracted into CH_2Cl_2 (×3). Standard drying and FCC (10-25% acetone/Et_2O gradient) monitored by TLC (*hRf* = 30 (8-*epi*-**15**), 20 (**15**) in Et_2O) gave 8-*epi*-**15** (8.4 mg, 25%) along with **15** as a clear resin (7.7 mg, 23%); $[\alpha]^{25}_D$ -19° (*c* 0.3, CH_2Cl_2); **FTIR (film):** 3468, 2944, 1727, 1237, 1162, 875 cm^{-1}; **^{1}H NMR ($CDCl_3$):** δ 7.41 (1H, br s, H-16), 7.39 (1H, t, *J* = 1.9 Hz, H-15), 6.38 (1H, dd, *J* = 1.9, 0.8 Hz, H-14), 5.52 (1H, dd, *J* = 11.7, 5.3 Hz, H-12), 5.15 (1H, dd, *J* = 12.3, 7.6

Hz, H-2), 3.94 (1H, dd, *J* = 10.3, 3.9 Hz, H-18a), 3.49 (1H, dd, *J* = 10.3, 8.0 Hz, H-18b), 2.54 (1H, ddd, *J* = 12.3, 7.0, 2.6 Hz, H-3a), 2.49 (1H, dd, *J* = 13.3, 5.3 Hz, H-11a), 2.17 (1H, d, *J* = 0.9 Hz, H-10), 2.16 (3H, s, OCOCH_3), 2.16 (1H, m, H-7a), 2.06 (1H, dd, *J* = 12.1, 3.0 Hz, H-8), 1.99 (1H, dt, *J* = 13.3, 3.3 Hz, H-6a), 1.89 (1H, m, H-4), 1.80 (1H, q, *J* = 12.3 Hz, H-3b), 1.64 (1H, dddd, *J* = 14.0, 13.5, 12.1, 3.4 Hz, H-7b), 1.58 (1H, ddd, *J* = 13.3, 11.7, 0.9 Hz, H-11b), 1.45 (3H, s, H-20), 1.43 (1H, m, H-6b), 0.96 (3H, s, H-19); **^{13}C NMR ($CDCl_3$):** δ 203.6 (C, C-1), 171.3 (C, C-17), 170.0 (C, O*C*OCH$_3$), 143.7 (CH, C-15), 139.4 (CH, C-16), 125.2 (C, C-13), 108.4 (CH, C-14), 76.0 (CH, C-2), 72.1 (CH, C-12), 64.5 (CH, C-10), 61.7 (CH_2, C-18), 51.5 (CH, C-8), 50.8 (CH, C-4), 43.4 (CH_2, C-11), 41.9 (C, C-5), 38.1 (CH_2, C-6), 35.3 (C, C-9), 31.8 (CH_2, C-3), 20.6 (CH_3, OCO*C*H$_3$), 18.1 (CH_2, C-7), 16.7 (CH_3, C-19), 15.3 (CH_3, C-20); **HRESIMS** [M + Na$^+$] *m/z* 427.1729 (calcd for $C_{22}H_{28}O_7Na^+$, 427.1727).

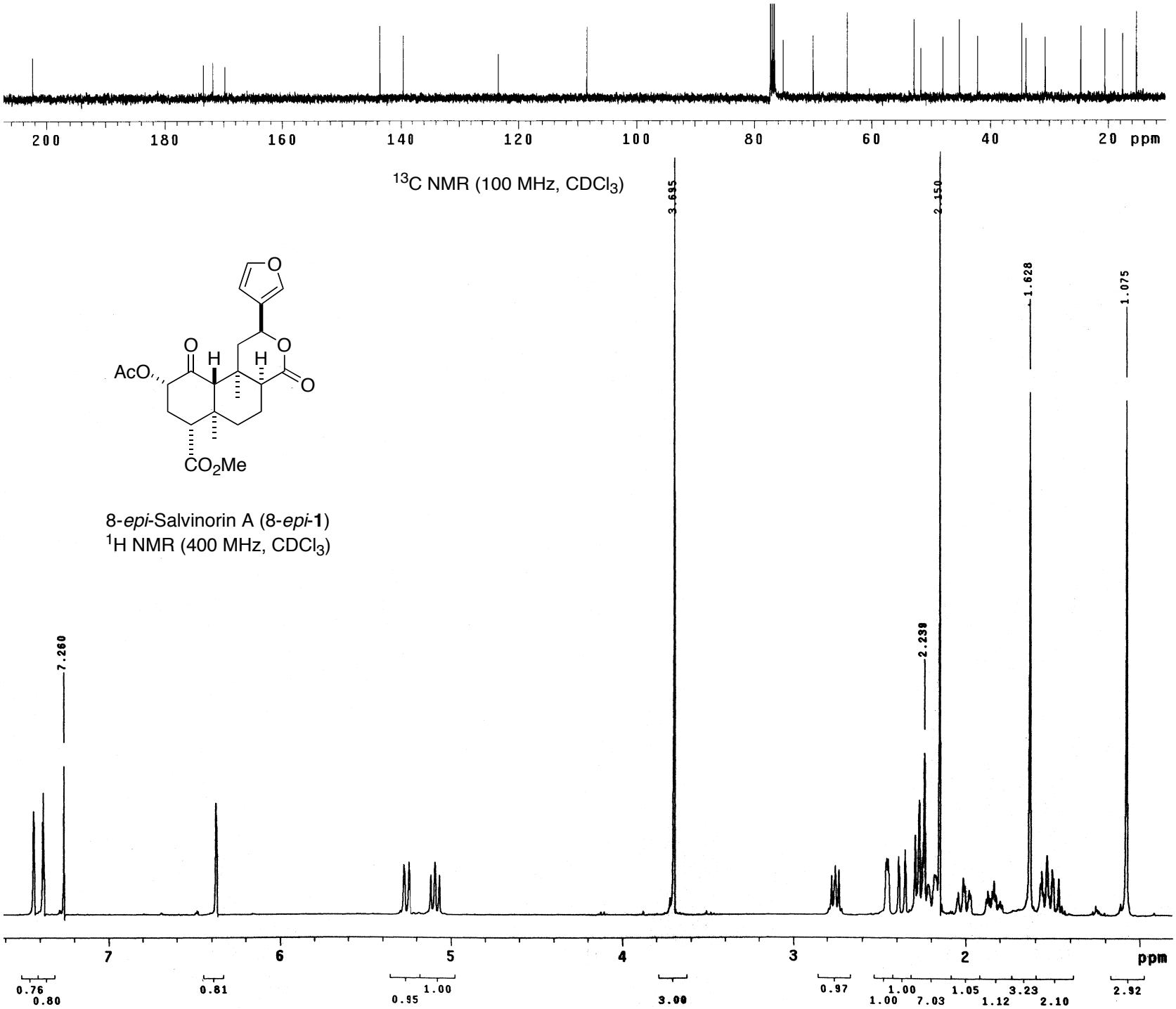
1-Deoxysalvinorin A (18). A solution of $NaBH_4$ (11.6 mg, 307 μmol) and **1** (108 mg, 249 μmol) in dry EtOH (9 mL)/CH_2Cl_2 (2 mL) was stirred under Ar at 40 °C. The cloudy solution gradually cleared. At 4 h, TLC indicated completion (*hRf* = 45 (**1**), 25 (8-*epi*-**7**), 14 (**7**) in Et_2O). The solution was evaporated in vacuo, and the residue partitioned between brine and CH_2Cl_2 (× 3). Standard drying gave an impure ~1:1 mixture of **7** and 8-*epi*-**7** (103 mg). This crude mixture and 1,1'-thiocarbonyldiimidazole (118 mg, 662 μmol) were dissolved in dry DMF and stirred under Ar at 90 °C for 6 h, when TLC indicated completion (*hRf* = 86 (**16**), 62 (**7**/8-*epi*-**7**) in 40% acetone/ CH_2Cl_2). The cooled solution was diluted in EtOAc/Et_2O and washed (10% HCl × 3, then brine). Standard drying followed by FCC (1-5% acetone/ CH_2Cl_2 gradient) gave the cyclic thionocarbonates **16** (H-8α:β, ~1:2), as a clear resin (72 mg, 67% over two steps). The thionocarbonate mixture was dissolved in dry toluene (2 mL). The resulting cloudy solution was stirred under Ar at 80 °C. A solution of freshly distilled Bu_3SnH (150 μL, 550 μmol) and AIBN (5.4 mg, 33 μmol) in dry toluene (2 mL) was added in small portions over 4 h; the solution gradually cleared. After a further 2 h, TLC indicated completion (*hRf* = 70 (byproduct), 55 (**16**), 20 (**17**/8-*epi*-**17**) in 10% acetone/ CH_2Cl_2). The solution was cooled and loaded directly onto silica gel, rinsing the flask with CH_2Cl_2 (× 2). Repeated FCC (50-70% EtOAc/petrol gradient) monitored by TLC (*hRf* = 47 (8-*epi*-**17**), 40 (**17**) in Et_2O) gave 8-*epi*-**17** (15.5 mg, 25%) along with **17** (13.5 mg, 22%) as a clear resin, which was dissolved in pyridine (0.3 mL) and Ac_2O (0.3 mL) with a crystal of DMAP. The solution was stirred at rt for 2.5 h, when TLC indicated completion (*hRf* = 74 (**18**) in Et_2O, visualized in $KMnO_4$), then evaporated in vacuo. FCC (60% Et_2O/*n*-pentane) gave **18** as a clear resin (12.3 mg, 82%); $[\alpha]^{21}_D$ -8° (*c* 0.1, CH_2Cl_2); **FTIR (film):** 2952, 1729, 1365, 1245, 1153, 1024, 875 cm^{-1}; **^{1}H NMR ($CDCl_3$):** δ 7.43 (1H, br s, H-16), 7.42 (1H, t, *J* = 1.8 Hz, H-15), 6.41 (1H, dd, *J* = 1.9, 1.0 Hz, H-14), 5.47 (1H, ddd, *J* = 11.2, 5.6, 0.7 Hz, H-12), 4.74 (1H, tt, *J* = 11.0, 5.5 Hz, H-2), 3.66 (3H, s, CO_2CH_3), 2.28 (1H, dd, *J* = 13.5, 5.9 Hz, H-11a), 2.18 (1H, dd, *J* = 10.9, 3.5 Hz, H-4), 2.15 (1H, dd, *J* = 10.0, 3.5 Hz, H-8), 2.09 (1H, dq, *J* = 14.2, 3.4 Hz, H-7a), 2.05 (3H, s, OCOCH_3), 1.92 (1H, m, H-1a), 1.89 (2H, m, H-3), 1.74 (1H, dt, *J* = 13.5, 3.3 Hz, H-6a), 1.65 (1H, m, H-7b), 1.64 (1H, dd, *J* = 13.6, 11.5 Hz, H-11b), 1.50 (1H, td, *J* = 12.8, 11.2 Hz, H-1b), 1.31 (1H, td, *J* = 13.6, 3.7 Hz, H-6b), 1.11 (3H, s, H-19), 1.10 (1H, dd, *J* = 12.9, 2.2 Hz, H-10), 1.06 (3H, s, H-20); **^{13}C NMR ($CDCl_3$):** δ 172.7 (C, C-18), 171.9 (C, C-17), 170.5 (C, O*C*OCH$_3$), 143.8 (CH, C-15), 139.4 (CH, C-16), 125.6 (C, C-13), 108.4 (CH, C-14), 71.8 (2 × CH, C-2 & 12), 54.2 (CH, C-4), 52.9 (CH, C-

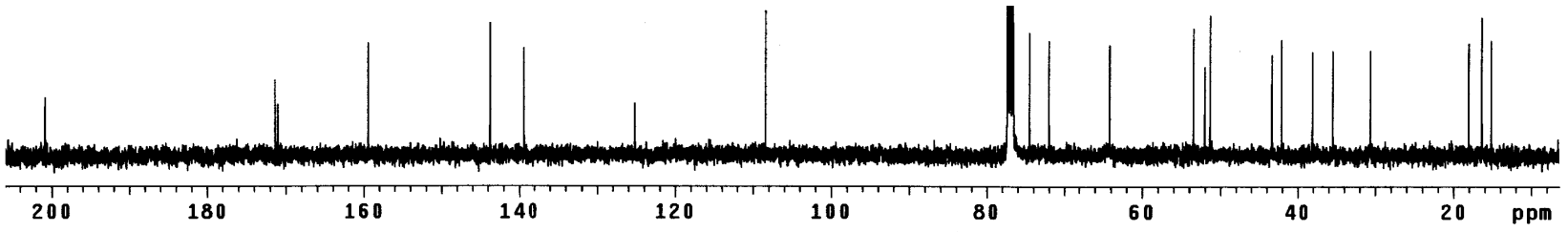
10), 51.5 (CH_3, CO_2CH_3), 51.2 (CH, C-8), 43.9 (CH_2, C-11), 38.0 (CH_2, C-6), 36.9 (C, C-9), 36.2 (C, C-5), 29.6 (CH_2, C-3), 26.7 (CH_2, C-1), 21.3 (CH_3, $OCOCH_3$), 18.2 (CH_2, C-7), 15.0 (CH_3, C-19), 14.6 (CH_3, C-20); **HRESIMS** [M + Na^+] *m/z* 441.1893 (calcd for $C_{23}H_{30}O_7Na^+$, 441.1884).

IUPAC/NIST Chemical Identifiers (INChIs):[6,7] **1,** 1.12Beta/C23H28O8/c1-12(24)30-16-9-15(20(26)28-4)22(2)7-5-14-21(27)31-17(13-6-8-29-11-13)10-23(14,3)19(22)18(16)25/h1-4H3,5H2,6H,7H2,8H,9-10H2,11H,14-17H,19H/t14-,15-,16-,17-,19-,22-,23-/m0/s1; 8-*epi*-**1,** 1.12Beta/C23H28O8/c1-12(24)30-16-9-15(20(26)28-4)22(2)7-5-14-21(27)31-17(13-6-8-29-11-13)10-23(14,3)19(22)18(16)25/h1-4H3,5H2,6H,7H2,8H,9-10H2,11H,14-17H,19H/t14-,15+,16+,17+,19+,22+,23+/m1/s1; **3,** 1.12Beta/C22H26O8/c1-21-6-4-13-20(26)30-16(12-5-7-28-10-12)9-22(13,2)18(21)17(24)15(29-11-23)8-14(21)19(25)27-3/h1-3H3,4H2,5H,6H2,7H,8-9H2,10-11H,13-16H,18H/t13-,14-,15-,16-,18-,21-,22-/m0/s1; **6,** 1.12Beta/C25H30O9/c1-13(26)32-18-10-17(22(28)30-5)24(3)8-6-16-23(29)34-19(15-7-9-31-12-15)11-25(16,4)21(24)20(18)33-14(2)27/h1-5H3,6H2,7H,8H2,9-10H,11H2,12H,16H,18-21H/t16-,18-,19-,20-,21-,24-,25-/m0/s1; **8,** 1.12Beta/C23H30O8/c1-12(24)30-16-9-15(20(26)28-4)22(2)7-5-14-21(27)31-17(13-6-8-29-11-13)10-23(14,3)19(22)18(16)25/h1-4H3,5H2,6H,7H2,8H,9-10H2,11H,14-19H,25H/t14-,15-,16-,17-,18-,19-,22-,23-/m0/s1; **9,** 1.12Beta/C25H32O9/c1-13(26)32-18-10-17(22(28)30-5)24(3)8-6-16-23(29)34-19(15-7-9-31-12-15)11-25(16,4)21(24)20(18)33-14(2)27/h1-5H3,6H2,7H,8H2,9H,10-11H2,12H,16-21H/t16-,17-,18-,19-,20-,21-,24-,25-/m0/s1; **10,** 1.12Beta/C23H32O8/c1-12(24)30-16-9-15(20(26)28-4)22(2)7-5-14-21(27)31-17(13-6-8-29-11-13)10-23(14,3)19(22)18(16)25/h1-4H3,5-11H2,13-17H,19H/t13u,14-,15-,16-,17-,19-,22-,23-/m0/s1; **11,** 1.12Beta/C23H30O8/c1-12(24)30-16-9-15(20(26)28-4)22(2)7-5-14-21(27)31-17(13-6-8-29-11-13)10-23(14,3)19(22)18(16)25/h1-4H3,5H2,6H,7H2,8H,9-10H2,11H,14-17H,19H,21H,27H/t14-,15-,16-,17-,19-,21u,22-,23-/m0/s1; **12,** 1.12Beta/C23H30O7/c1-13(24)30-17-9-16(21(26)27-4)22(2)7-5-15-12-29-18(14-6-8-28-11-14)10-23(15,3)20(22)19(17)25/h1-4H3,5H2,6H,7H2,8H,9-10H2,11H,12H2,15-18H,20H/t15-,16-,17-,18-,20-,22-,23-/m0/s1; **13,** 1.12Beta/C23H28O7/c1-13(24)30-17-9-16(21(26)27-4)22(2)7-5-15-12-29-18(14-6-8-28-11-14)10-23(15,3)20(22)19(17)25/h1-4H3,5H2,6H,7H2,8H,9-10H2,11-12H,16-18H,20H/t16-,17-,18-,20-,22-,23-/m0/s1; **15,** 1.12Beta/C22H28O7/c1-12(24)28-16-8-14(10-23)21(2)6-4-15-20(26)29-17(13-5-7-27-11-13)9-22(15,3)19(21)18(16)25/h1-3H3,4H2,5H,6H2,7H,8-10H2,11H,14-17H,19H,23H/t14-,15-,16-,17-,19-,21-,22-/m0/s1; **18,** 1.12Beta/C23H30O7/c1-13(24)29-15-9-17(20(25)27-4)22(2)7-5-16-21(26)30-18(14-6-8-28-12-14)11-23(16,3)19(22)10-15/h1-4H3,5H2,6H,7H2,8H,9-11H2,12H,15-19H/t15-,16-,17-,18-,19-,22-,23-/m0/s1.

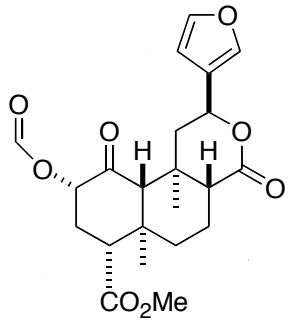
1. Roth, B. L.; Baner, K.; Westkaemper, R.; Siebert, D.; Rice, K. C.; Steinberg, S.; Ernsberger, P.; Rothman, R. B. Salvinorin A: A potent naturally occurring nonnitrogenous κ opioid selective agonist. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11934-11939.
2. Glennon, R. A.; Lee, M.; Rangisetty, J. B.; Dukat, M.; Roth, B. L.; Savage, J. E.; McBride, A.; Rauser, L.; Hufeisen, S.; Lee, D. K. 2-Substituted tryptamines: agents with selectivity for 5-HT_6 serotonin receptors. *J. Med. Chem.* **2000**, *43*, 1011-1018.
3. NIMH Psychoactive Drug Screening Program. http://pdsp.cwru.edu (accessed Oct 2004).

4. Chavkin, C.; Sud, S.; Jin, W.; Stewart, J.; Zjawiony, J. K.; Siebert, D. J.; Toth, B. A.; Hufeisen, S. J.; Roth, B. L. Salvinorin A, an Active Component of the Hallucinogenic Sage *Salvia divinorum* Is a Highly Efficacious κ-Opioid Receptor Agonist: Structural and Functional Considerations. *J. Pharmacol. Exp. Ther.* **2004**, *308*, 1197-1203.
5. Pauwels, P. J.; Colpaert, F. C. Heterogeneous ligand-mediated Ca^{++} responses at wt and mutant α_{2A}-adrenoceptors suggest multiple ligand activation binding sites at the α_{2A}-adrenoceptor. *Neuropharmacology* **2000**, *39*, 2101-2111.
6. IUPAC-NIST Chemical Identifier Project. http://www.iupac.org/projects/2000/2000-025-1-800.html (accessed Oct 2004).
7. World Wide Molecular Matrix Service: Generate INChI. http://wwmm.ch.cam.ac.uk/sdf2inchi/index.html (accessed Oct 2004).


200
180
160
140
120
100
80
60
40
20 ppm
13C NMR (100 MHz, CDCl3)
3.695
2.150
1.628
1.075
AcO
O
H
H
O
O
O
CO2Me
8-epi-Salvinorin A (8-epi-1)
1H NMR (400 MHz, CDCl3)
7.260
2.239
7
6
5
4
3
2
ppm
0.76
0.80
0.81
0.95
1.00
3.00
0.97
1.00
1.00
7.03
1.05
1.12
3.23
2.10
2.92

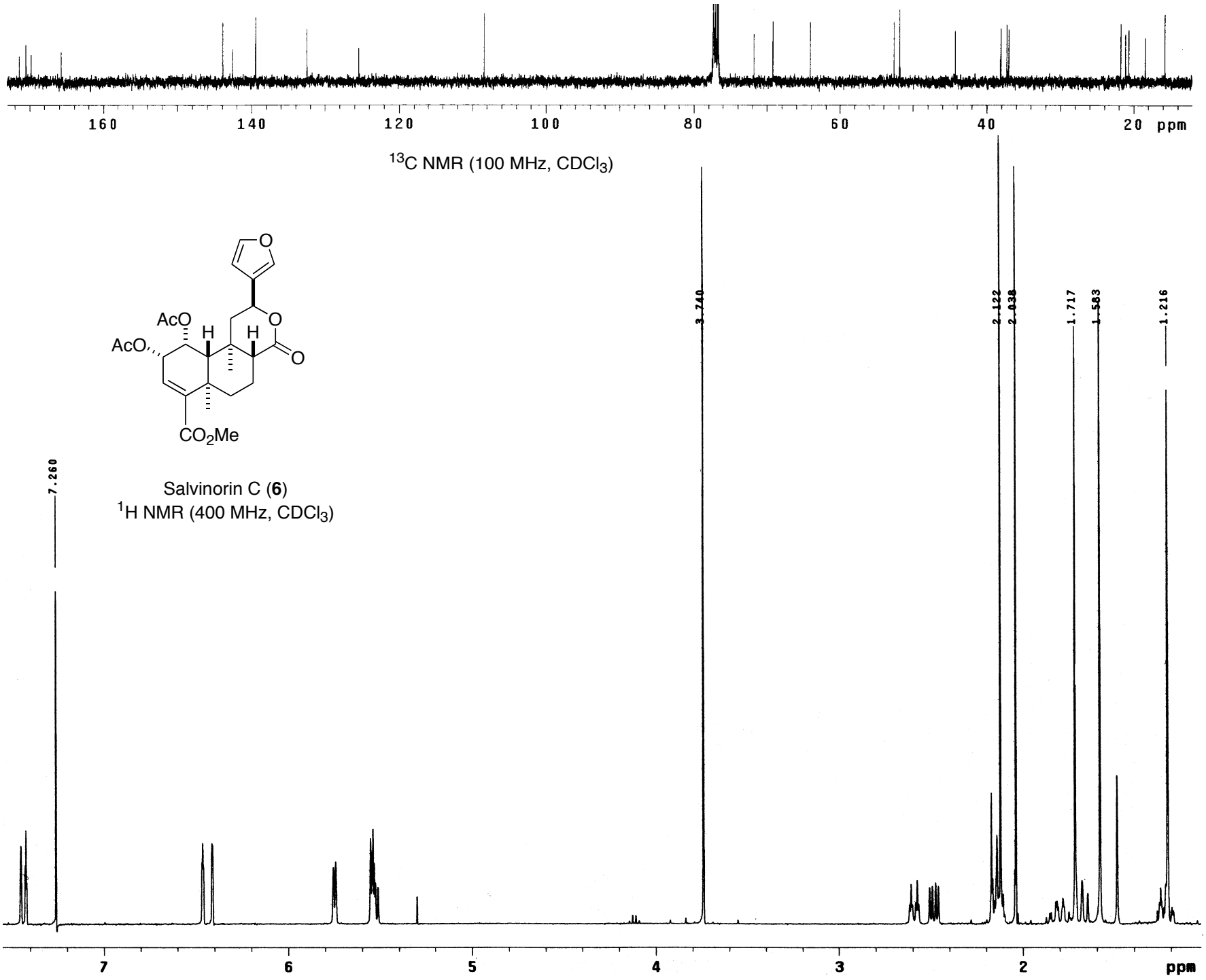


^{13}C NMR (100 MHz, $CDCl_3$)



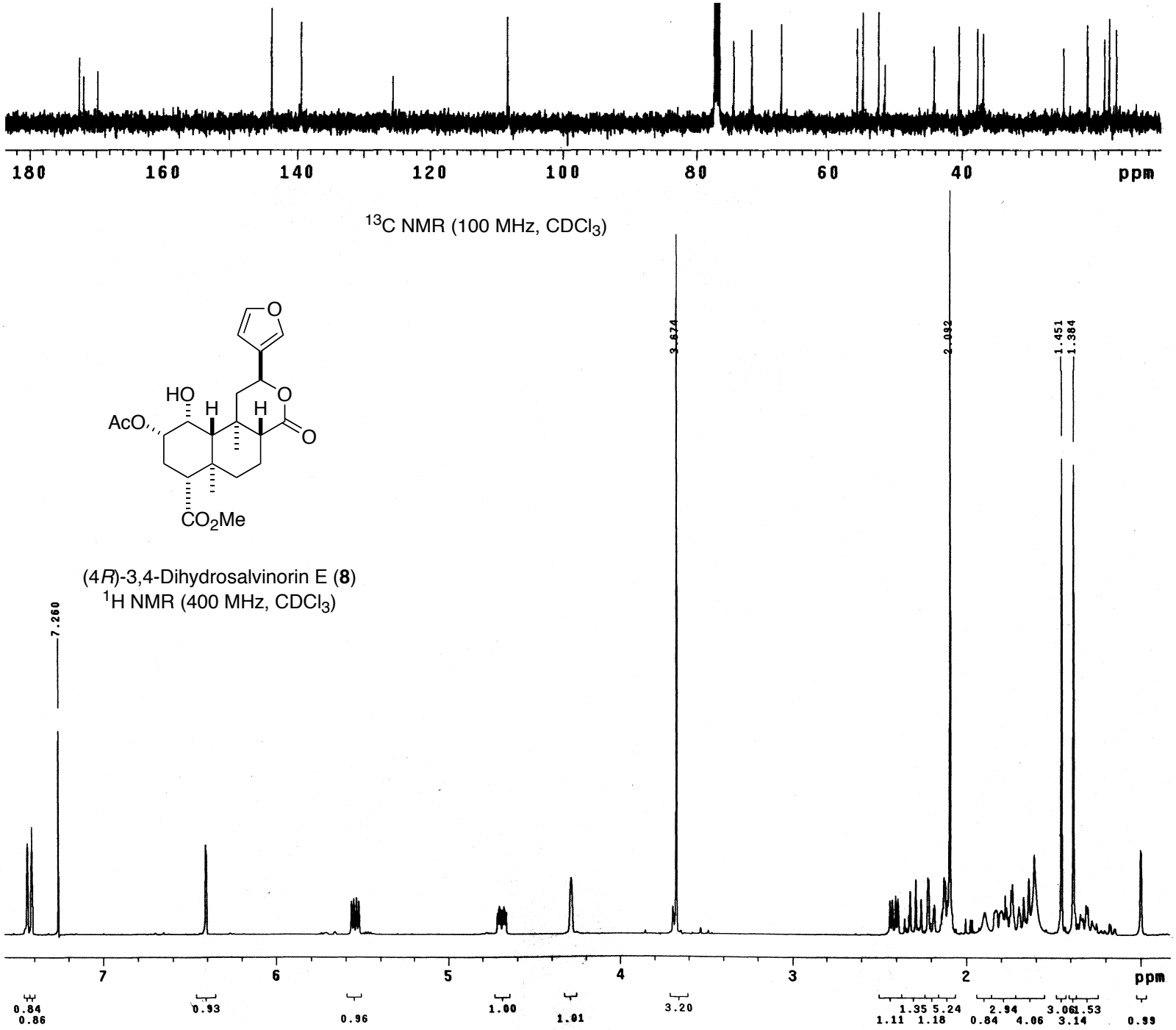
Salvinorin B formate (**3**)

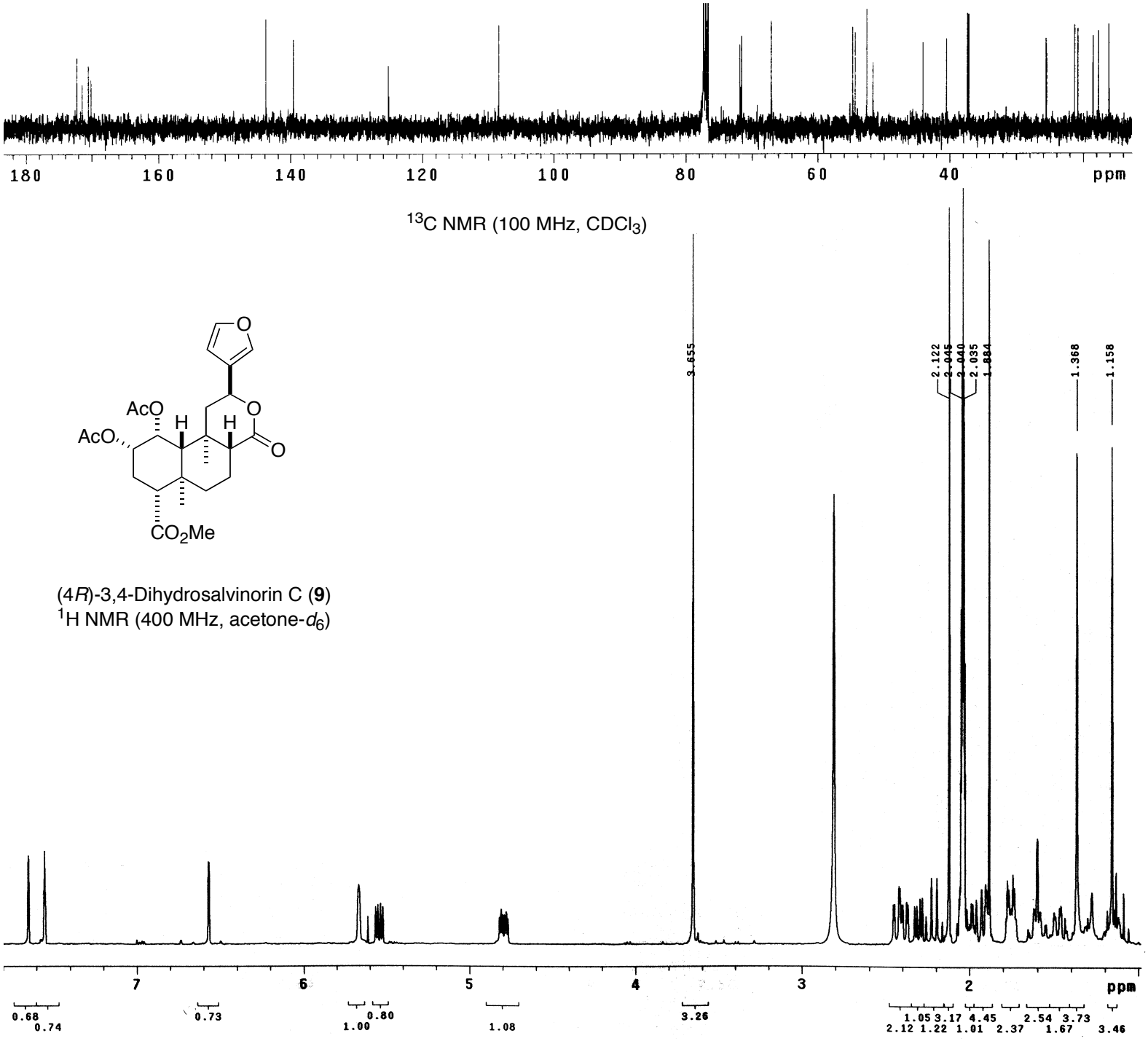
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

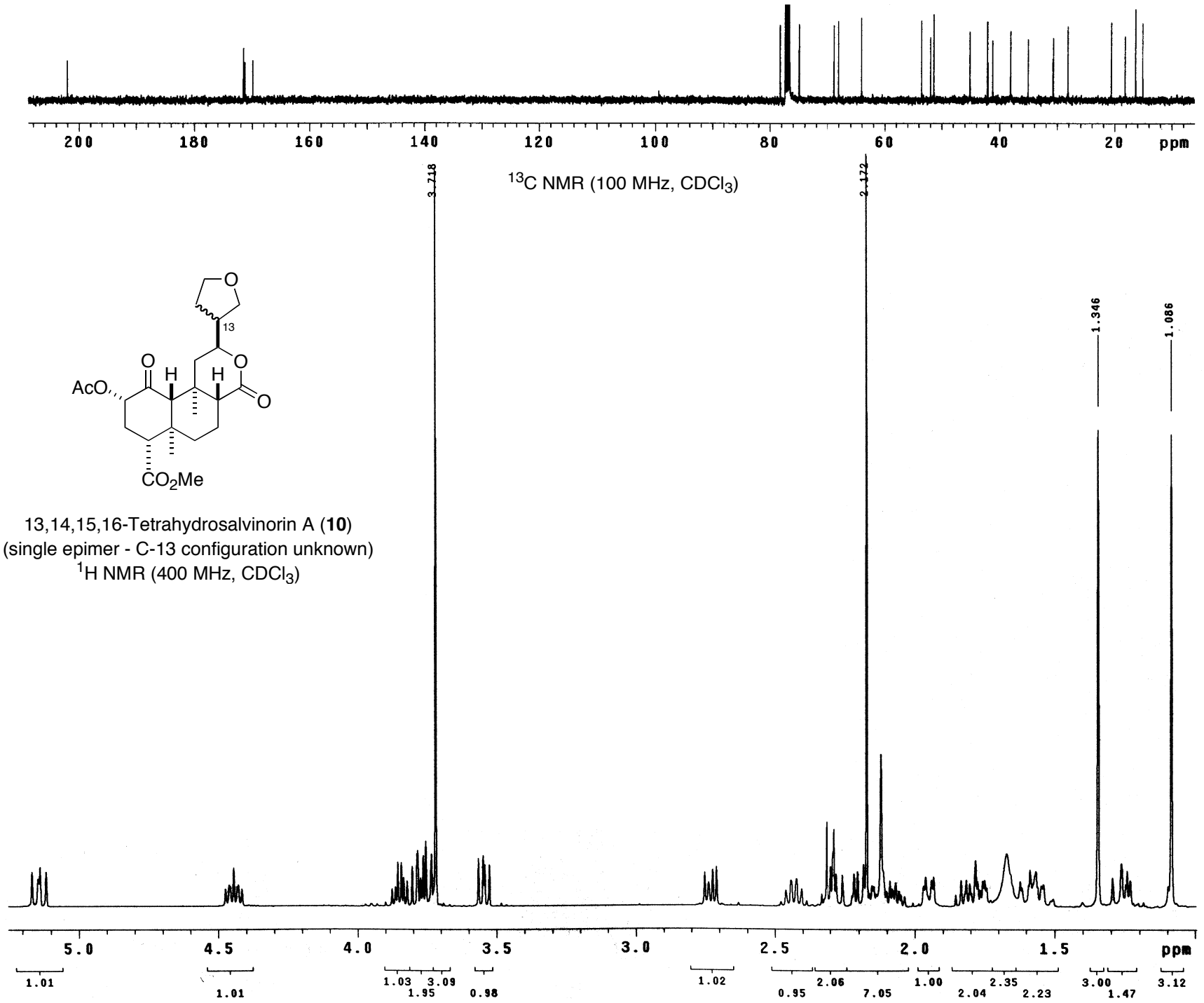
Salvinorin C (**6**)
^{1}H NMR (400 MHz, $CDCl_3$)


180
160
140
120
100
80
60
40
ppm
^{13}C NMR (100 MHz, $CDCl_3$)
HO
H
H
AcO
O
O
O
CO_2Me
(4*R*)-3,4-Dihydrosalvinorin E (**8**)
^{1}H NMR (400 MHz, $CDCl_3$)
7.260
3.674
2.032
1.451
1.384
7
6
5
4
3
2
ppm
0.84
0.86
0.93
0.96
1.00
1.01
3.20
1.35
1.11
5.24
1.18
2.94
0.84
4.06
3.06
3.14
1.53
0.99

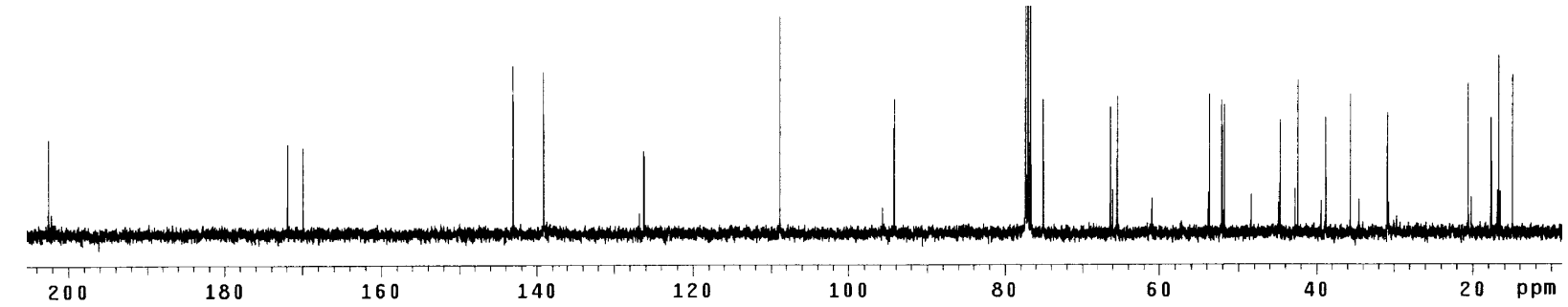


^{13}C NMR (100 MHz, $CDCl_3$)

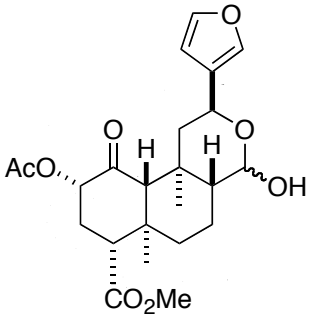
(4*R*)-3,4-Dihydrosalvinorin C (**9**)
^{1}H NMR (400 MHz, acetone-d_6)



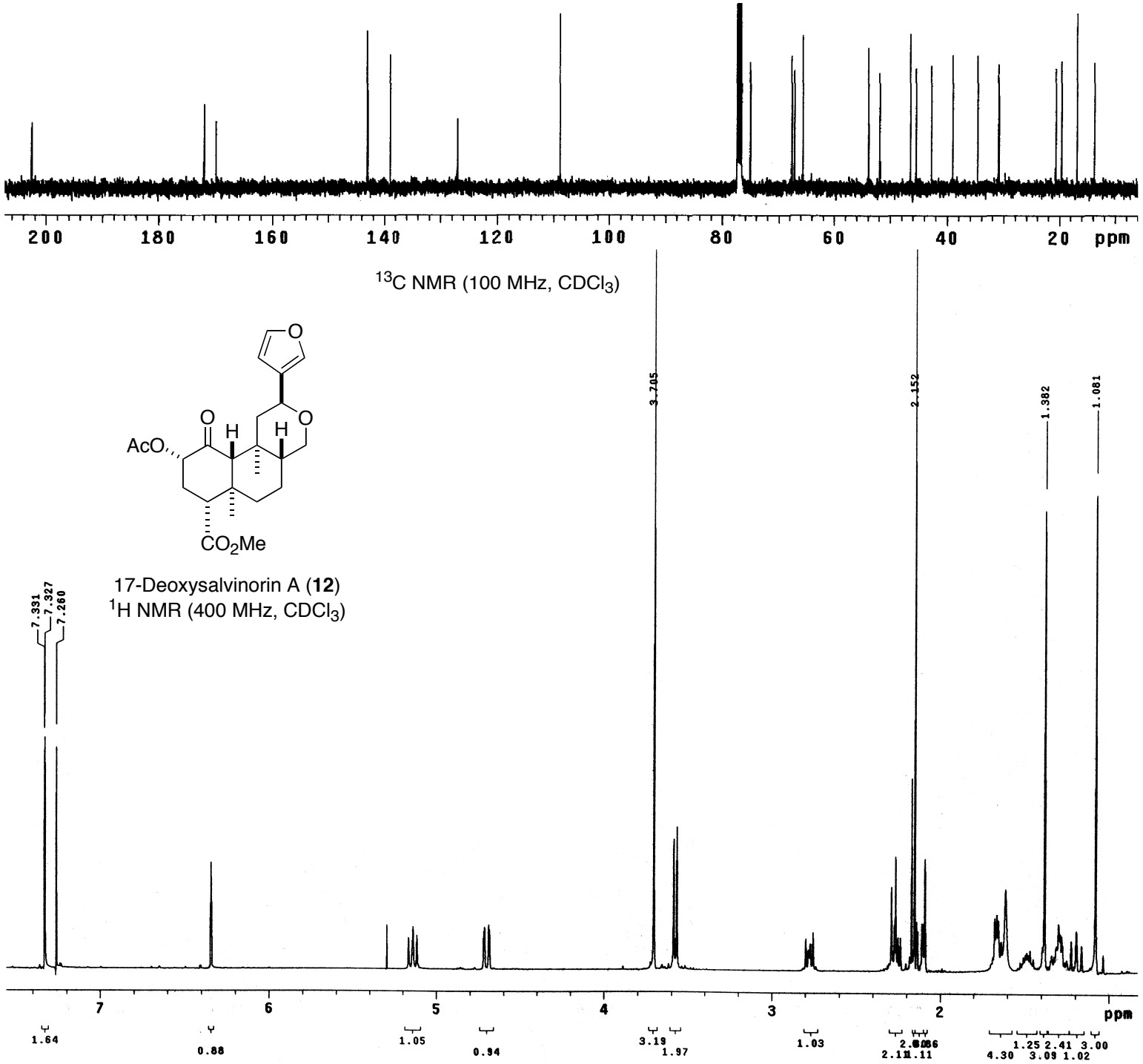
13,14,15,16-Tetrahydrosalvinorin A (**10**)
(single epimer - C-13 configuration unknown)
^{1}H NMR (400 MHz, $CDCl_3$)

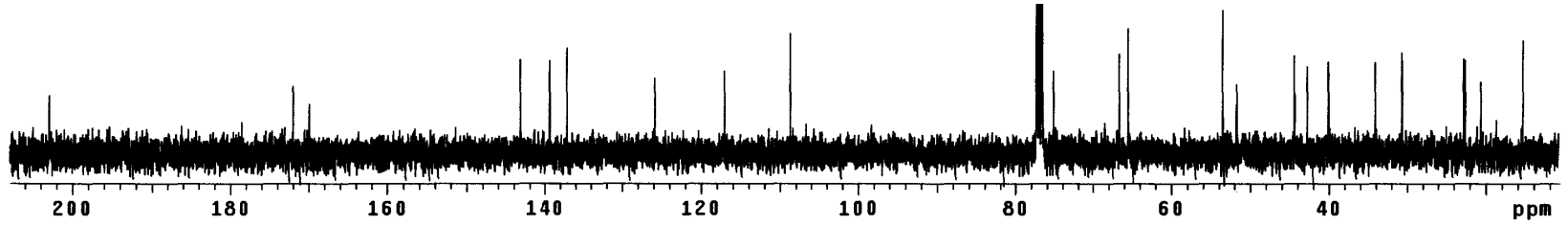


^{13}C NMR (100 MHz, $CDCl_3$)

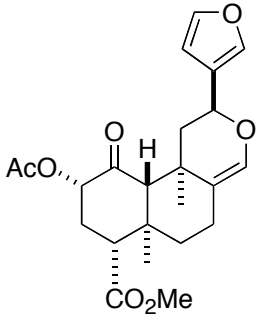


Salvinorin A lactol (**11**)
^{1}H NMR (400 MHz, $CDCl_3$)

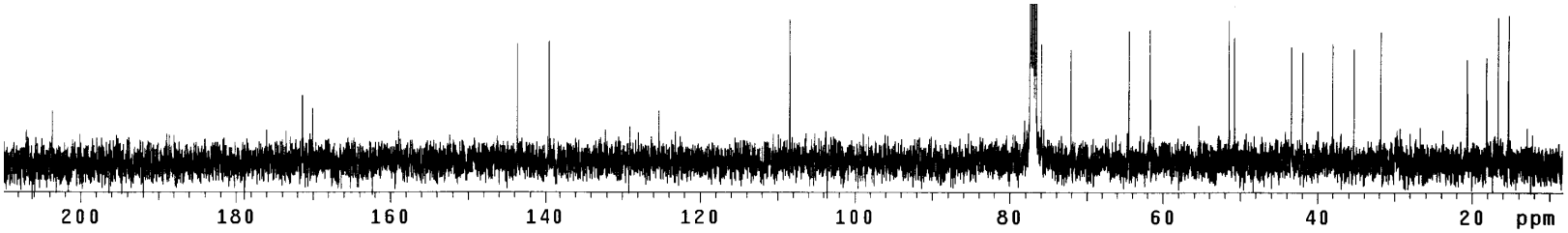

200
180
160
140
120
100
80
60
40
20
ppm
13C NMR (100 MHz, CDCl3)
O
O
H
H
O
AcO
CO2Me
17-Deoxysalvinorin A (12)
1H NMR (400 MHz, CDCl3)
7.331
7.327
7.260
3.705
2.152
1.382
1.081
7
6
5
4
3
2
ppm
1.64
0.88
1.05
0.94
3.19
1.97
1.03
2.11
1.11
4.30
1.25
3.09
2.41
1.02
3.00



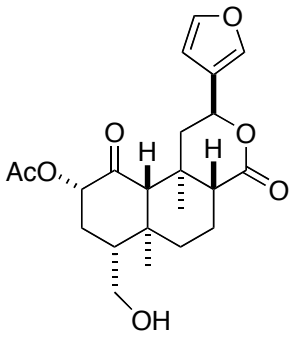
^{13}C NMR (100 MHz, $CDCl_3$)



8,17-Didehydro-17-deoxysalvinorin A (**13**)
^{1}H NMR (400 MHz, $CDCl_3$)

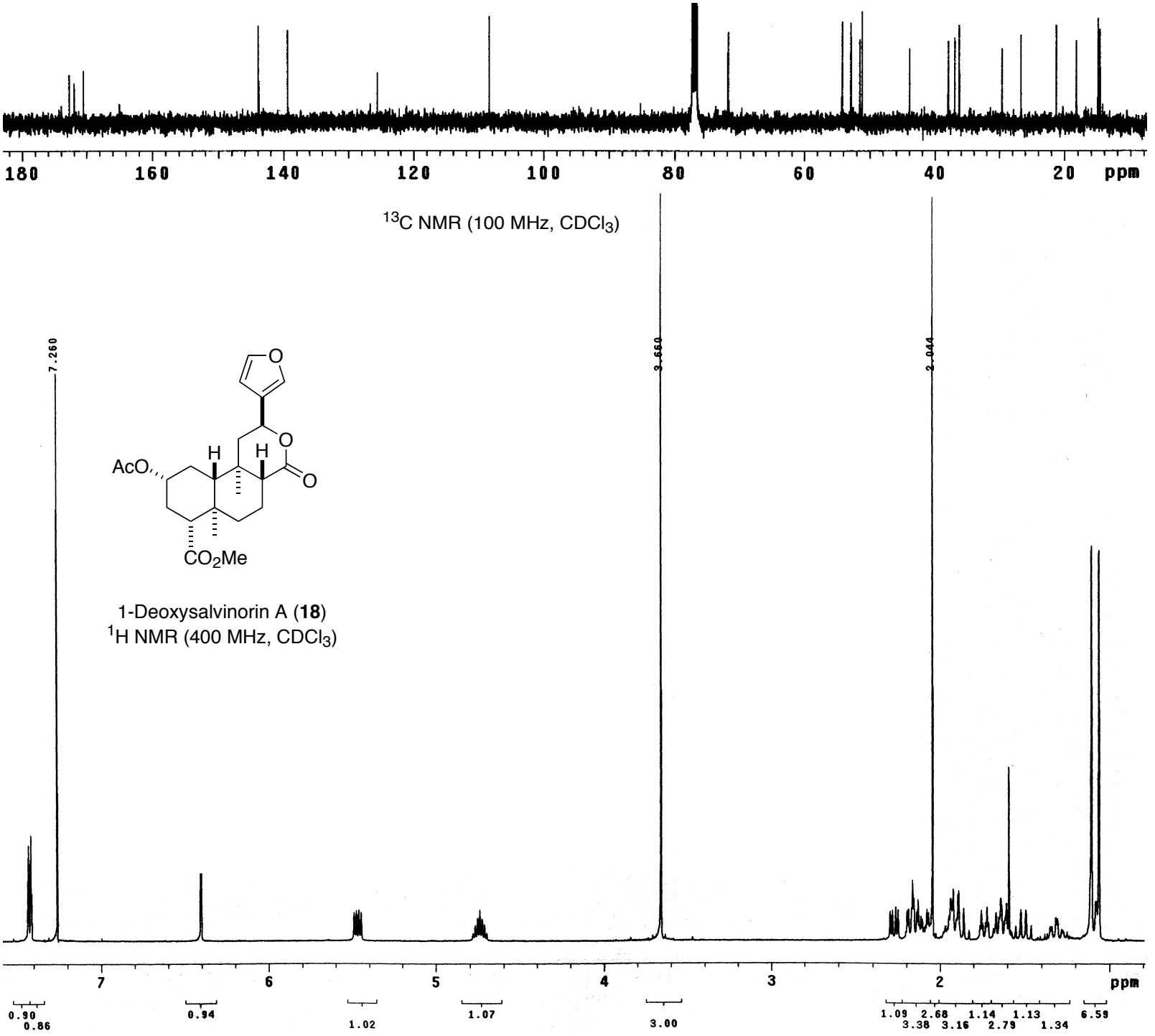


^{13}C NMR (100 MHz, $CDCl_3$)



O-Demethyl-18-deoxysalvinorin A (**15**)

^{1}H NMR (400 MHz, $CDCl_3$)


180
160
140
120
100
80
60
40
20
ppm
^{13}C NMR (100 MHz, $CDCl_3$)
7.260
3.660
2.044
AcO
H
H
O
O
O
CO_2Me
1-Deoxysalvinorin A (**18**)
^{1}H NMR (400 MHz, $CDCl_3$)
7
6
5
4
3
2
ppm
0.90
0.86
0.94
1.02
1.07
3.00
1.09
2.68
1.14
1.13
3.38
3.16
2.79
1.34
6.59